Inventor: Terrance P. SNUTCH et al.
Title: CALCIUM CHANNEL INHIBITORS COMPRISING BENZHYDRIL SPACED FROM PIPERAZINE

PATENT Docket 381092000624

Com- pound	Name	Structure
P1	6,6-Bis-(4-fluoro-phenyl)- 1-[4-(2-phenylsulfanyl- ethyl)-piperazin-1-yl]- hexan-1-one	S-NN-F
P2	1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-[2-(4- fluoro-phenoxy)-ethyl]- piperazine	F F
P3	1-{4-[2- (Benzo[1,3]dioxol-5- yloxy)-ethyl]-piperazin-1- yl}-6,6-bis-(4-fluoro- phenyl)-hexan-1-one	H-CI F
P4	l-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-(2- phenylsulfanyl-ethyl)- piperazine	s—NNN
P5	l-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-[2-(4- methoxy-phenoxy)-ethyl]- piperazine	MeO—O N N N H—CI H—CI

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Com- pound	Name	Structure
Р6	1-{4-[2-(2,4-Difluoro- phenoxy)-ethyl]- piperazin-1-yl}-6,6-bis- (4-fluoro-phenyl)-hexan- 1-one	F O N N N N N N N N N N N N N N N N N N
P7	6,6-Bis-(4-fluoro-phenyl)- 1-[4-(2-phenoxy-ethyl)- piperazin-1-yl]-hexan-1- one	F F
P8	1-{4-[2-(2,4-Dichloro- phenoxy)-ethyl]- piperazin-1-yl}-6,6-bis- (4-fluoro-phenyl)-hexan- 1-one	F CI
P9	6,6-Bis-(4-fluoro-phenyl)- 1-{4-[2-(4-methoxy- phenoxy)-ethyl]- piperazin-1-yl}-hexan-1- one	MeO—O N N F
P10	1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-(2- phenoxy-ethyl)-piperazine	F F

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Com- pound	Name	Structure
P11	6,6-Bis-(4-fluoro-phenyl)- 1-{4-[2-(3,4,5-trimethoxy-phenoxy)-ethyl]- piperazin-1-yl}-hexan-1- one	MeO O O O O O O O O O O O O O O O O O O
P12	1-{4-[2-(Benzothiazol-2-ylsulfanyl)-ethyl]- piperazin-1-yl}-6,6-bis- (4-fluoro-phenyl)-hexan- 1-one	S N S F
P13	[4-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-piperazin-1-yl}-ethoxy)-2,3,6-trimethyl-phenyl]-carbamic acid tert-butyl ester	H N P
P14	4-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-ethoxy)-2,3,6-trimethyl-phenylamine	$\begin{array}{c c} & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & &$
P15	1-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-4-[2-(2,4-dichloro-phenoxy)-ethyl]-piperazine	CI F

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Com- pound	Name	Structure
P16	[2-(4-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-ylmethyl}-2,6-di-tert-butyl-phenoxy)-ethyl]-dimethylamine	H-CI H-CI H-CI F
P17	4-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-ylmethyl}-2,6-di-tert-butyl-phenol	HO H-CI H-CI H-CI
P18	1-[4-(3,5-Di-tert-butyl-4-methoxy-benzoyl)-piperazin-1-yl]-6,6-bis-(4-fluoro-phenyl)-hexan-1-one	MeO F
P19	1-[4-(3,5-Di-tert-butyl-4-methoxy-benzyl)-piperazin-1-yl]-6,6-bis-(4-fluoro-phenyl)-hexan-1-one	MeO F
P20	1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-(3,5-di- tert-butyl-4-methoxy- benzyl)-piperazine	H-CI H-CI

Figure 1

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 $P\quad A\quad T\quad E\quad N\quad T$ Docket 381092000624

Com- pound	Name	Structure
P21	{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-(3,5-di-tert-butyl-4-methoxy-phenyl)-methanone	MeO F
P22	1-{4-[3,5-Di-tert-butyl-4-(2-dimethylamino-ethoxy)-benzoyl]-piperazin-1-yl}-6,6-bis-(4-fluoro-phenyl)-hexan-1-one	J J J J J J J J J J J J J J J J J J J
P23	1-Benzo[1,3]dioxol-5- ylmethyl-4-[6,6-bis-(4- fluoro-phenyl)-hexyl]- piperazine	F H-CI H-CI F
P24	1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-(3,5-di- tert-butyl-benzyl)- piperazine	H-CI H-CI F
P25	{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-(3,5-di-tert-butyl-4-hydroxy-phenyl)-methanone	HO F

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Com- pound	Name	Structure
P26	1-[4-(3,5-Di-tert-butyl-4- hydroxy-benzyl)- piperazin-1-yl]-6,6-bis-(4- fluoro-phenyl)-hexan-1- one	HO
P27	1-[4-(3,5-Dibromo-4-hydroxy-benzoyl)-piperazin-1-yl]-6,6-bis-(4-fluoro-phenyl)-hexan-1-one	Br N N F
P28	1-[4-(3,5-Di-tert-butyl-4-hydroxy-benzoyl)-piperazin-1-yl]-6,6-bis-(4-fluoro-phenyl)-hexan-1-one	HO F
P29	1-[4-(3,5-Di-tert-butyl-benzoyl)-piperazin-1-yl]-6,6-bis-(4-fluoro-phenyl)-hexan-1-one	F
P30	1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-(4-tert- butyl-benzyl)-piperazine	H-CI H-CI F

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	<u> </u>	
Com- pound	Name	Structure
P31	1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-(9H- thioxanthen-9-yl)- piperazine	S P N N P F
P32	2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-benzothiazole	H-CI H-CI
P33	6,6-Bis-(4-fluoro-phenyl)- 1-(4-pyrimidin-2-yl- piperazin-1-yl)-hexan-1- one	H-CI F
P34	2-{4-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-piperazin- 1-yl}-pyrimidine	F H-CI H-CI
P35	6,6-Bis-(4-fluoro-phenyl)- 1-[4-(9H-thioxanthen-9- yl)-piperazin-1-yl]-hexan- 1-one	S N N N F

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Com- pound	Name	Structure
P36	1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-(3,4,5- trimethoxy-benzyl)- piperazine-2-carboxylic acid ethyl ester	MeO NeO F
P37	6,6-Bis-(4-fluoro-phenyl)- 1-{4-[2-(3,4,5-trimethoxy-benzylamino)-ethyl]- piperazin-1-yl}-hexan-1- one	MeO H N N N N N N N N N N N N N N N N N N
P38	9,9-Bis-(4-fluoro-phenyl)- 1-[4-(3,4,5-trimethoxy- benzyl)-piperazin-1-yl]- nonan-1-one	H-CI O OMe OMe OMe
P39	(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-ethyl)-phenyl-amine	
P40	1-[9,9-Bis-(4-fluoro- phenyl)-nonyl]-4-(3,4,5- trimethoxy-benzyl)- piperazine	H-CI OMe OMe F

Figure 1

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Com- pound	Name	Structure
P41	(4-{4-[Bis-(4-fluoro-phenyl)-methoxy]-butyl}-piperazin-1-yl)-(3,4,5-trimethoxy-phenyl)-methanone	OMe MeO H-CI MeO N N
P42	6,6-Bis-(4-fluoro-phenyl)- 1-[4-(4-trifluoromethoxy- benzoyl)-piperazin-1-yl]- hexan-2-one	F F N N N N N N N N N N N N N N N N N N
P43	1-[4-(4-Bromo-benzoyl)- piperazin-1-yl]-6,6-bis-(4- fluoro-phenyl)-hexan-1- one	Br F
P44	6,6-Bis-(4-fluoro-phenyl)- 5-hydroxy-1-[4-(3,4,5- trimethoxy-benzoyl)- piperazin-1-yl]-hexan-1- one	MeO OH F
P45	1-{4-[Bis-(4-fluoro- phenyl)-methoxy]-butyl}- 4-(3,4,5-trimethoxy- benzyl)-piperazine	OMe H-CI H-CI MeO N N

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Com- pound	Name	Structure
P46	6,6-Bis-(4-fluoro-phenyl)- 6-hydroxy-1-[4-(3,4,5- trimethoxy-benzoyl)- piperazin-1-yl]-hexan-1- one	MeO NOME
P47	4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-1-(3,4,5-trimethoxy-benzyl)-piperazine-2-carboxylic acid	MeO NeO OH
P48	4-[6,6-Bis-(4-fluoro- phenyl)-hexanoyl]-1- (3,4,5-trimethoxy- benzyl)-piperazin-2-one	MeO OMe F
P49	1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-4-(3,5-di-tert-butyl-4-methoxy-benzoyl)-piperazin-2-one	MeO F
P50	1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-(3,4,5- trimethoxy-benzoyl)- piperazin-2-one	MeO OMe

Figure 1

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Com- pound	Name	Structure
P51	4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-1-(3,4,5-trimethoxy-benzyl)-piperazin-2-one	MeO OMe F
P52	4-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-1-(3,5-di-tert-butyl-4-methoxy-benzyl)-piperazin-2-one	MeO F
P53	4-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-1-[2-(4-fluoro-phenoxy)-ethyl]-piperazin-2-one	F O O O O O O O O O O O O O O O O O O O
P54	1-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-4-(3,5-di-tert-butyl-4-methoxy-benzoyl)-piperazin-2-one	MeO F
P55	4-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-1-(3,5-di-tert-butyl-4-methoxy-benzoyl)-piperazin-2-one	MeO F

Figure 1

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Com- pound	Name	Structure
P56	1-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-4-(3,5-di-tert-butyl-4-methoxy-benzyl)-piperazin-2-one	MeO F
P57	1-[6,6-Bis-(4-fluoro- phenyl)-hexanoyl]-4-(3,5- di-tert-butyl-4-hydroxy- benzoyl)-piperazin-2-one	HO P
P58	6,6-Bis-(4-fluoro-phenyl)- 1-[4-(3,4,5-trimethoxy- benzoyl)-piperazin-1-yl]- hex-5-en-1-one	F F
P59	1-{4-[2-(3,4-Dimethoxy-phenoxy)-ethyl]-piperazin-1-yl}-6,6-bis-(4-fluoro-phenyl)-hexan-1-one	N N N N N N N N N N N N N N N N N N N
P60	1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-[2-(3,4- dimethoxy-phenoxy)- ethyl]-piperazine	F F

Figure 1

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Com- pound	Name	Structure
P61	1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4- (3,4,5-trimethoxy- benzyl)-piperazine-2- carboxylic acid	OMe OMe OMe N OMe
P62	4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-1-(3,4,5-trimethoxy-benzyl)-piperazine-2-carboxylic acid ethylester	OMe OMe OMe
P63	1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-(3,4- dimethoxy-benzyl)- piperazine	OMe N N F
P64	1-[4-(3,4-Dimethoxy-benzoyl)-piperazin-1-yl]-6,6-bis-(4-fluoro-phenyl)-hexan-1-one	OMe OME F
P65	1-[2- (Benzo[1,3]dioxol-5- yloxy)-ethyl]-4-[6,6- bis-(4-fluoro-phenyl)- hexyl]-piperazine	

Figure 1

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Com- pound	Name	Structure
P66	1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-[2- (3,4,5-trimethoxy- phenoxy)-ethyl]- piperazine	OMe OME OME F
P67	1-(4-Amino-2,3,5- trimethyl-phenoxy)-3- {4-[6,6-bis-(4-fluoro- phenyl)-hexyl]- piperazin-1-yl}- propan-2-ol	H _M N N N N N N N N N N N N N N N N N N N
P68	1-{4-[3-(4-Amino-2,3,5-trimethyl-phenoxy)-2-hydroxy-propyl]-piperazin-1-yl}-6,6-bis-(4-fluoro-phenyl)-hexan-1-one	H _M N N N N N N N N N N N N N N N N N N N
P69	1-(4-Benzothiazol-2- yl-piperazin-1-yl)-6,6- bis-(4-fluoro-phenyl)- hexan-1-one	N N N N N N N N N N N N N N N N N N N
P70	1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-(3,5- bis-trifluoromethyl- benzyl)-piperazine	F F F

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Com- pound	Name	Structure
P71	1-[4-(3,5-Bis- trifluoromethyl- benzoyl)-piperazin-1- yl]-6,6-bis-(4-fluoro- phenyl)-hexan-1-one	
P72	1-[4-(4-tert-Butyl- benzoyl)-piperazin-1- yl]-6,6-bis-(4-fluoro- phenyl)-hexan-1-one	
P73	1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-(4- bromo-benzyl)- piperazine	Br F
P74	2-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-ethylsulfanyl)-benzothiazole	S N N N N N N N N N N N N N N N N N N N
P75	6,6-Bis-(4-fluoro- phenyl)-1-[4-(4- hydroxy-3,5- dimethoxy-benzoyl)- piperazin-1-yl]-hexan- 1-one	OMe HOOME

Figure 1

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Com- pound	Name	Structure
P76	4-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-ylmethyl}-2,6-dibromo-phenol	Br N N F
P77	1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-(4- trifluoromethoxy- benzyl)-piperazine	F F N N N N N N N N N N N N N N N N N N
P78	(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-ethyl)-(3,4,5-trimethoxy-benzyl)-amine	OMe H N N N N N N N N N N N N N N N N N N
P79	1-{4-[2-(4-Fluoro- phenoxy)-ethyl]- piperazin-1-yl}-6,6- bis-(4-fluoro-phenyl)- hexan-1-one	F F
P80	6,6-Bis-(4-fluoro- phenyl)-1-[4-(2- phenylamino-ethyl)- piperazin-1-yl]-hexan- 1-one	F F

Figure 1

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Com- pound	Name	Structure
P81	1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-[2- (2,4-difluoro- phenoxy)-ethyl]- piperazine	F C F
P82	N-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-2-oxoethyl)-benzamide	
P83	N-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-2-oxo-ethyl)-4-chlorobenzamide	
P84	N-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-2-oxo-ethyl)-4-methyl-benzamide	CH,
P85	N-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-2-oxo-ethyl)-4-isopropyl-benzamide	

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Compound	Name	Structure
P86	N-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-2-oxo-ethyl)-4-tert-butyl-benzamide	F N N N N N N N N N N N N N N N N N N N
P87	N-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-2-oxo-ethyl)-4-fluoro-benzamide	F N N
P88	N-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-piperazin-1-yl}-2-oxo-ethyl)-benzamide	F N N N N N N N N N N N N N N N N N N N
P89	N-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-piperazin-1-yl}-2-oxo-ethyl)-4-chloro-benzamide	F N N N N N N N N N N N N N N N N N N N

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Com- pound	Name	Structure
P90	N-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-piperazin-1-yl}-2-oxo-ethyl)-4-methyl-benzamide	H CH ₃
P91	N-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-piperazin-1-yl}-2-oxo-ethyl)-4-isopropyl-benzamide	
P92	N-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-piperazin-1-yl}-2-oxo-ethyl)-4-tert-butyl-benzamide	
P93	N-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-piperazin-1-yl}-2-oxo-ethyl)-4-fluoro-benzamide	

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Com- pound	Name	Structure
P94	1-[4-(2-Benzylamino- ethyl)-piperazin-1-yl]- 6,6-bis-(4-fluoro- phenyl)-hexan-1-one	
P95	1-{4-[2-(4-Chloro- benzylamino)-ethyl]- piperazin-1-yl}-6,6- bis-(4-fluoro-phenyl)- hexan-1-one	
P96	6,6-Bis-(4-fluoro- phenyl)-1-{4-[2-(4- methyl-benzylamino)- ethyl]-piperazin-1-yl}- hexan-1-one	\$\frac{2}{\fin}}{\frac{2}{\firn}}{\firn}}}}}}{\frac{\frac{2}{\frac{2}{\frac{2}{\frac{2}{\frac
P97	6,6-Bis-(4-fluoro- phenyl)-1-{4-[2-(4- isopropyl- benzylamino)-ethyl]- piperazin-1-yl}-hexan- 1-one	

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Com- pound	Name	Structure
P98	1-{4-[2-(4-tert-Butyl- benzylamino)-ethyl]- piperazin-1-yl}-6,6- bis-(4-fluoro-phenyl)- hexan-1-one	
P99	1-{4-[2-(4-Fluoro- benzylamino)-ethyl]- piperazin-1-yl}-6,6- bis-(4-fluoro-phenyl)- hexan-1-one	
P100	6,6-Bis-(4-fluoro- phenyl)-1-[4-(1- hydroxy-pyridine-4- carbonyl)-piperazin-1- yl]-hexan-1-one	HO N
P101	4-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-ylmethyl}-2,6-dimethoxy-phenol	OMe HO OMe

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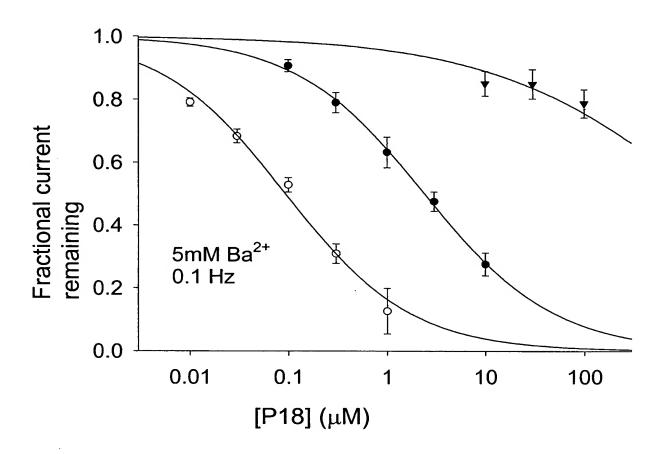
$P \quad A \quad T \quad E \quad N \quad T$ Docket 381092000624

Com- pound	Name	Structure
P102	9,9-Diphenyl-1-[4- (3,4,5-trimethoxy- benzyl)-piperazin-1- yl]-nonan-1-one	OMe OMe OMe OMe
P103	1-[4-(3,5-Di-tert-butyl-4-methoxy-benzoyl)-2-methyl-piperazin-1-yl]-6,6-bis-(4-fluoro-phenyl)-hexan-1-one	OMe N N N N N N N N N N N N N N N N N N N
P104	1-[4-(3,5-Di-tert-butyl-4-methoxy-benzoyl)-3-methyl-piperazin-1-yl]-6,6-bis-(4-fluoro-phenyl)-hexan-1-one	OMe N N
P105	1-[4-(3,5-Di-tert-butyl-benzoyl)-2-methyl-piperazin-1-yl]-6,6-bis-(4-fluoro-phenyl)-hexan-1-one	
P106	1-[4-(4-tert-Butyl- benzoyl)-2-methyl- piperazin-1-yl]-6,6- bis-(4-fluoro-phenyl)- hexan-1-one	

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Selectivity of P18 for various calcium channels



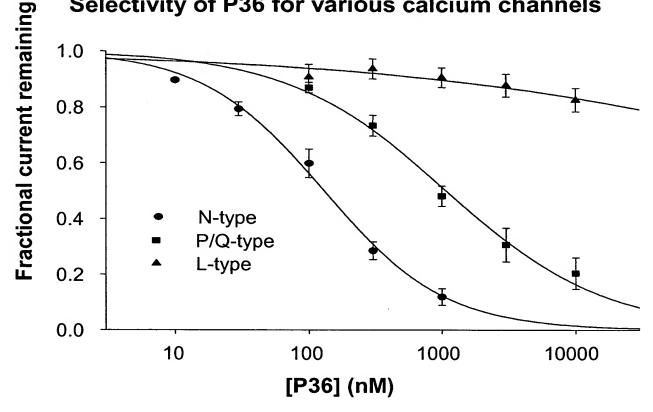
- N-type $IC_{50} = 0.11 \pm 0.02 \,\mu\text{M} \,(n=5)$ 0
- P/Q-type IC₅₀ = $2.71 \pm 0.28 \mu M$ (n=5)
- $IC_{50} >> 100 \mu M (n=5)$ L-type

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Selectivity of P36 for various calcium channels



N-type IC50 =
$$136 \pm 13$$
 nM (n=6)

$$P/Q$$
-type $IC50 = 920 \pm 123 \text{ nM} \text{ (n=5)}$

L-type IC50 >>> 10
$$\mu$$
M (n=5)

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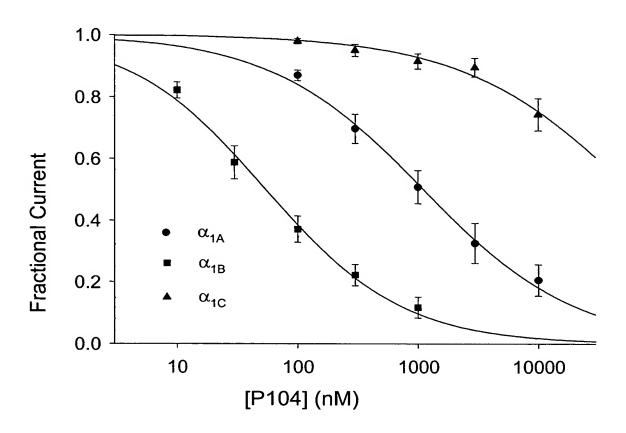
Inventor: Terrance P. SNUTCH et al.

Title: CALCIUM CHANNEL INHIBITORS COMPRISING

BENZHYDRIL SPACED FROM PIPERAZINE

P A T E N T Docket 381092000624

Effect of P104 on Various HVA Ca2+ Channels



P/Q-type $IC_{50} = 1659 \pm 811$ nM (n=5)

N-type $IC_{50} = 61 \pm 11 \text{ nM (n=5)}$

L-type $IC_{50} >> 10 \mu M$ (n=5) (estimate : 144 μM)

Figure 4